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Bioavailability of Soil-borne Chemicals: A Regulatory Perspective

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ABSTRACT

U.S. Environmental Protection Agency (USEPA) risk assessment guidance documents dating back to 1989 have articulated the principles for incorporating information on bioavailability into the risk assessment process. However, in the interim period both the methods for obtaining media or route specific measures of bioavailability and the corresponding guidance to incorporate these data have languished. Presently, USEPA is developing guidance to address both of these concerns. This article outlines the broad framework for systematically evaluating the role of bioavailability in site-specific risk assessment from a regulatory perspective. At the same time, in appreciation of the vast horizon of uncharted territory ahead, the focus of USEPA's draft guidance, and consequently this report, is on bioavailability adjustments for soil-borne metals. The article describes a two-stage process. The first stage outlines a paradigm for screening sites to determine if generating site-specific data on the bioavailability of a metal in soil is of technical utility and economically justifiable. The second stage focuses on the collection, analysis, and incorporation of these data into the risk assessment for decision-making purposes.

Key Words: metals, soil, bioavailability, risk assessment, regulatory decisions.

INTRODUCTION

The role of bioavailability in risk assessment has been addressed in various U.S. Environmental Protection Agency (USEPA) guidance documents dating back from the Risk Assessment Guidance for Superfund (RAGS) Human Health Evaluation Manual (Part A, USEPA 1989) to the more recent Risk Assessment Guidance for Superfund Human Health Evaluation Manual (Part E—Dermal Risk assessment, USEPA 2001a). Appendix A (Adjustment for Absorption Efficiency) of RAGS, Part

The regulatory perspective described herein is extracted from draft guidance currently under development by a USEPA workgroup on bioavailability. The workgroup is chaired by Mike Beringer (USEPA, Region 7) and receives technical support from Gary Diamond (Syracuse Research Corporation).

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A details the common scenarios in which bioavailability factors into the risk assessment process. The first scenario addresses route-to-route adjustment of toxicity factors from administered to absorbed dose. The example provided to illustrate this adjustment involves dermal exposure assessment. The paradigm in RAGS, Part A for assessing risk from the dermal exposure pathway gives rise to an estimate of absorbed dose. Due to the current lack of route specific toxicity criteria (*i.e.*, Cancer Slope Factors and Reference Doses) for the dermal pathway, risk estimates are based on coupling oral toxicity criteria to estimates of absorbed dose. Oral toxicity factors are typically based on studies where the dose metric is recorded in terms of administered rather than absorbed dose. Correction of the toxicity factors from administered to absorbed dose is conceptually straightforward; however, simplistic adjustments can be confounded when combining exposure from one exposure pathway (*e.g.*, dermal) with toxicity criteria from another pathway (*e.g.*, oral). For example, a chemical may be significantly metabolized by the first-pass effect in the portal circulation when administered orally. If the toxicity of the chemical was mediated through a toxic metabolite, this information may need to be considered when adjusting the toxicity factor from administered to absorbed dose. Such would be the case if the chemical in question were not significantly metabolized when entering the systemic circulation by the dermal route. In this case, the process for adjusting the toxicity factor as outlined in Appendix A of RAGS, Part A (*i.e.*, focusing on the fraction of the parent compound in the systemic circulation rather than the rate and extent of toxic metabolite generation) could result in an inappropriate value for assessment of dermal risks.

In contrast to the earlier example, the use of bioavailability data to adjust dose is more straightforward when the medium or vehicle for exposure rather the exposure route is at issue. As exemplified in RAGS, Part A (Section A-3) information on bioavailability can be useful when the exposure medium in a risk assessment differs from the conditions employed in the critical study to develop the toxicity factor. Perhaps the most salient example of this phenomenon is in matching a toxicity factor developed from a critical study where absorption was high (*e.g.*, highly water-soluble contaminant in an aqueous medium) to a medium (*e.g.*, soil) where absorption of the chemical is either known or anticipated to be much lower. In this case, obtaining the bioavailability of the chemical from the medium of interest relative to that of the critical study will reduce uncertainty and strengthen the risk assessment.

In keeping with the aforementioned discussion, USEPA is developing guidance (in draft form at the time of this manuscript's submission) that is focused on bioavailability adjustments between exposure media (*e.g.*, water and soil).

SCOPE

As previously noted, bioavailability guidance under development by USEPA is concentrating on adjustments between exposure media rather than exposure route. Specifically, the focus is on the bioavailability of metals in soil. However, the basic concepts and principles applied to soil-borne metals will have general applicability to other media (*e.g.*, sediment, food), chemical classes (*e.g.*, semi-volatiles) and exposure routes (*e.g.*, dermal, inhalation).

Guidance on bioavailability will likely have application in a number of USEPA programs engaging in hazardous site assessments including Resource Conservation and Recovery Act (RCRA) corrective actions, Superfund removal and remedial sites, the Underground Storage Tank program, and Brownfield sites.

BIOAVAILABILITY ADJUSTMENT SCREENING PROTOCOL

USEPA (1989) describes the basic premise for making bioavailability adjustments; however, this document does not provide detailed guidance on how to assess site-specific bioavailability, or on how to decide when such assessments should be pursued in support of site risk assessments. Guidance under development by USEPA will provide a framework for evaluating and incorporating bioavailability information into a risk-based, decision-making process.

The role of bioavailability in risk assessment is best approached through sequential stages. The first stage should provide a process for deciding whether additional data collection and analysis is likely to improve the basis for making decisions at a site in a cost effective manner. The second stage should provide a process for collecting, analyzing and incorporating additional bioavailability data into the site-specific risk assessment.

Stage I, Step1. Assessment of current and potential future risk at a site is typically performed utilizing default assumptions of bioavailability for contaminants of concern including soil-borne metals. In effect, this amounts to a bioavailability of one (100%) relative to the bioavailability in the critical study that formed the basis for a particular chemical's toxicity factor.[1] If risks are below a level of concern based on use of default assumptions, it is generally appropriate to conclude that no further investigation is needed. When such a situation is not apparent, it is then important to readily determine if additional information on bioavailability would be useful so as to avoid substantial delays in the risk assessment process.

Stage I, Step 2. The second step involves assembling all the available relevant data from the site under consideration or from other similar sites that may be useful in judging whether the bioavailability of the metal in soil at the site could be substantially different from the default value used in screening-level calculations described earlier. Information would likely include type of site and origin of the metal contamination, soil chemistry, and data on the chemical form of the metal in the soil. These data might be derived from samples collected from the site or from historical knowledge about the sources of soil contamination. Data providing a characterization of the soil type(s) at a site may also be assembled with specific attention paid to those features that are known or suspected to affect solubility of the metal. In general, these would include the organic content, mineral composition, pH, cation exchange, and the physical characteristics of the metal-soil complex (*e.g.*, particle size distribution). The types of information that would be relevant for particular metals should be assessed from the available scientific literature. Further discussion of these topics can be found in NRC (2002) and USEPA (2002a). The ultimate goal of this step is to

[1]Medium-specific absorption default values are currently available for lead; and medium-specific Reference Doses have been developed for cadmium and manganese.

provide a plausible bounding estimate for the absolute or relative bioavailability of the soil-borne metal at the site for use in the sensitivity analysis detailed in the next step.

Stage I, Step 3. This step involves assessing the sensitivity of risk estimates to plausible assumptions about site-specific bioavailability. The purpose of sensitivity assessment is to determine whether further collection and evaluation of data on site-specific bioavailability are likely to have a significant impact on risk estimates or risk-based decisions at a site. Both site-specific information and data gathered from the scientific literature are used to develop a plausible range of bioavailability values. This range of values would be used in the risk equations to determine the plausible magnitude of changes in risk (*e.g.*, Hazard Quotient or excess lifetime cancer risk) that occurs when different assumptions are made about relative bioavailability within the plausible range.

Superfund guidance on probabilistic risk assessment (USEPA 2001b) details a variety of analytical approaches to sensitivity analysis. The range of methods differs widely in complexity. In the simplest approach, values assigned to the relative bioavailability parameter would be varied across the plausible range with a estimate of risk obtained for each value. Although simple to execute, this method may not accurately reflect the sensitivity of the risk estimate to the bioavailability parameter when plausible bounds are considered for other parameters. Methods of sensitivity analysis that utilize Monte Carlo analysis are available in which values of multiple parameters can be varied simultaneously, and the relative contribution of each parameter can be assessed. The value added by these more sophisticated probabilistic methods will depend on the form and complexity of the risk equations. See the aforementioned guidance on probabilistic risk assessment (USEPA 2001b) for a more detailed discussion on the advantages and limitations of various approaches to sensitivity analysis.

Stage I, Step 4. At this step, based on data collected and evaluated in previous steps, an assessment should be made whether decision-making at the site would be significantly impacted by plausible alternative values for bioavailability. For example, if the results of the sensitivity analysis indicate that risk-based decisions might change if alternative bioavailability values were used in the risk assessment, then collecting additional information to support a site-specific value for bioavailability may be warranted. Conversely, such efforts would serve little purpose if, even at the extremes of the plausible bounds on bioavailability, risk-based decisions were unlikely to be impacted. Such would be the case at a site with soil-borne metal contamination so uniformly high that no plausible bioavailability adjustment would change the need for remediation. Another factor to consider is whether collecting site-specific bioavailability information is justified by its potential remedial cost savings. The changes in remedial scope secondary to a bioavailability adjustment may not warrant the additional costs associated with obtaining the adjustment at a very small site. Finally, consideration should be given to the possibility that bioavailability of the soil-borne metal may be highly variable across the site. In such cases the alternative values of bioavailability may not be applicable to all exposure units (*i.e.*, a geographic area for which a risk estimate is to be made).

Stage I, Step 5. This last step in Stage I addresses the level of scientific support associated with the methods/models available for generating the particular bioavailability

data needed for a site-specific bioavailability adjustment. The application of bioavailability data to the risk assessment process is presently in its nascent stages, thus standardized approaches for characterizing site-specific bioavailability are in short supply. Still, the potential modification of a soil clean-up goal based on bioavailability needs to meet a high burden of proof. Use of validated models best suits this objective. This is especially true in the case where *in vitro* assays or other types of extraction tests, the results of which are predicated on an established correlation with an animal bioassay, are being relied on. Model development typically proceeds from the research to the regulatory phase. The level of validation distinguishes these phases. General criteria for test models to gain regulatory acceptance are provided in ICCVAM (1997). The level of model/method validation may determine how prominently the results of bioavailability data are to be featured in the risk assessment. In general, regulatory models would best support revisions to the risk assessment that impact decision-making at the site. It may be more appropriate to feature results from models/methods enjoying less vigorous scientific support/validation in the Uncertainly Analysis section of the risk assessment with a qualitative/semi-quantitative discussion of uncertainty.

COLLECTING, ANALYZING AND INCORPORATING BIOAVAILABILITY DATA

Stage II, Step 1. If the deliberations in Stage I support collection and analysis of additional data the assessment proceeds to Stage II. This stage outlines the process for planning, executing, and documenting the data collection and analyses that would support site-specific measures of bioavailability and for integrating this information into the characterization of risk at a site. The first step in this process is to identify the appropriate methods/models for estimating site bioavailability. Factors to consider include data quality and degree of model validation as per the guidelines outlined in ICCVAM (1997). The documentation should summarize the pertinent results of these evaluations and why these results support the use of the model for the intended application at the site. Limitations of the selected model for the intended application, in comparison to alternatives, should also be documented. This step should also include detailed information for translating results into estimates of absolute or relative bioavailability. For example, if statistical transformations of the data, such as regression models, are to be used in translating the data output from the model into bioavailability estimates, these statistical methods should be adequately documented. The plan should also specify the required sample size needed to ensure a reliable estimate of bioavailability

Stage II, Step 2. After a test method (*e.g.*, bioassay) has been decided on, the application of this test method across the site needs to reviewed. In cases where the factors that influence the bioavailability of soil-borne metals (see Stage I, Step 2) are relatively uniform across a site, the results of a bioavailability study may be accordingly extrapolated. In other cases, the bioavailability of the metal of concern may vary within or across exposure units. In these cases, bioavailability should be assessed in representative samples from exposure units where variability is suspected or known to exist.

Stage II, Step 3. The plan for collecting data (sample collection, laboratory procedures, data handling, and archiving) to support site-specific bioavailability should be consistent with applicable guidance for data quality objectives (USEPA 2000a–c; USEPA 2002b–d).

Stage II, Step 4. In this final step, results of the site-specific bioavailability assessment are incorporated into the risk characterization. This process is consistent with Superfund guidance (USEPA 1989, 1991), which recommends that, in general, high quality site-specific parameter values are to be preferred over default values, which may not represent site conditions. As noted in Stage II, Step 1, the level of validation in the methods/models employed to estimate site-specific bioavailability will strongly influence whether risk estimates previously calculated using default values are re-estimated using site-specific values and featured in the body of the risk assessment, or if these results constitute a semi-quantitative discussion in the Uncertainty Analysis section of the risk assessment. In either event, the Uncertainty Analysis section should discuss the confidence in the site-specific estimate(s) of bioavailability, the limitations in the estimates and issues related to extrapolating these results over time.

NEXT STEPS

To support its draft directive on bioavailability, USEPA also plans to issue supporting guidance on the following topics: (1) guidance on evaluating methodologies for estimating site-specific bioavailability of metals in soil; (2) guidance on sampling designs in support of site-specific bioavailability assessments; (3) specific guidance on methodologies for assessing relative bioavailability of lead and arsenic in soil; and (4) default values for relative bioavailability of other metals. The USEPA also plans to provide review and consultation on site-specific bioavailability assessments conducted within the Agency and will make the results of these reviews available as they are completed.

The aforementioned guidance will be developed in concert with ongoing efforts within the Agency to develop recommendations and guidance for risk assessment of metals in general. The latter effort includes the Metals Action Plan (USEPA 2002a), which is being developed with the following objective:

> to establish a process for assessing hazard and risk for metals, state-of-the-science application of methods and data, a transparent process (i.e., articulating assumptions/uncertainties), and the flexibility to address program-specific areas.

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